REMARKS

Applicants note the Examiner's reminder regarding the proper format for amending the claims and express their gratitude to the Examiner for entering the amendments submitted on February 23, 2007. Claims 1, 13, 15, 16 and 20 have been further amended herein to more clearly define that which applicants believe to be their invention and to address the various 35 USC 112 objections the Examiner has raised as detailed below. The amendments to the claims do not introduce any new matter.

The Examiner has objected to the amendment originally submitted on October 6, 2005 as introducing new matter. In particular, the Examiner contends that the incorporation by reference of European application EP 01118812.5 introduces new matter. Applicants respectfully traverse the Examiner's conclusion, but in an effort to advance the prosecution of the application, applicants have amended the specification to remove the incorporation by reference statement, thus rendering the objection moot.

Claims 13 stands rejected under 37 CFR 1.75(c), the Examiner contending that claim 13 adds a new element to the invention of claim 1, contrary to the "closed" transitional language used in claim 1. Claim 13 has been rewritten to place the claim in independent form to overcome the rejection. The amendment is believed to fully address the rejection of claim 13 under 37 CFR 1.75(c).

Claim 15 is objected to for failing to specify, in the body of the claim, that the microparticles are polystyrene microparticles. Applicants have amended the body of the claim to specify that the microparticles are polystyrene microparticles, consistent with the preamble. The amendment is believed to fully address the rejection of claim 15 under 37 CFR 1.75(c).

Claims 1-3, 5, 9, 11-13 and 15-20 stand rejected under 35 USC 112, first paragraph as failing to comply with the written description requirement. Applicants address each of these rejections individually as follows.

Claims 1 and 15 stand rejected by the Examiner for the inclusion of the term "about" when referencing the relevant pH range associated with claims 1 and 15. First of all applicants note that claim 15 has been amended to recite a pH range of about 10.5 to about 12.5 and thus objected terminology is identical for both claims 15 and claim 1. Support for that pH range is found in paragraph [0030] (last two sentences).

The Examiner notes that the inclusion of the term "about" broadens the scope of the claim "so as to include pH values of, for example, pH 13.5". Applicants, while agreeing that a range of "about 10.5 to about 12.5" is broader than a range of "10.5 to 12.5", respectfully traverse the Examiner's assertion that the broader range would encompass a pH value as high as 13.5, and respectfully submit that the recitation of a range of 10.5 to 12.5 provides a written description of the range about 10.5 to about 12.5 fully compliant with the standard of 35 USC 112, second paragraph.

First of all the Examiner apparently fails to appreciate that the pH scale represents a reverse logarithmic representation of relative hydrogen proton (H+) concentration. Unlike linear scales that progress in a smooth, incremental manner, a shift in value on the pH scale represents a tenfold difference in H+ concentration. For example, a shift in pH from 2 to 3 represents a 10-fold decrease in H+ concentration. Thus the (H+) concentration of a solution at pH 12.5 is 5×10^{-12}, whereas the hydrogen concentration of a solution at pH 13.5 is 5×10^{-13}. Accordingly a solution at pH 13.5 has 10X the amount of (H+) as a solution at pH 12.5. Applicants respectfully submit that no person skilled in the art would consider a pH of 13.5 to be "about" the same as a pH of 12.5.

The inclusion of the term "about" is simply an effort by applicants to capture the experimental variance that is associated with any measurement. Applicants respectfully submit that one of ordinary skill would readily appreciate that the pH values recited in the specification would inherently include a certain degree of experimental error associated with them, such that applicants had possession of more than those exact numerical values as their claimed invention at the time the application was filed. In this regard applicants refer the Examiner to the US Guidelines for application of the Written Description requirement (http://www.uspto.gov/web/menu/written.pdf), and in particular, applicants note the Decision Tree on page 6 of those Guidelines. When a claim amendment arguably broadens the scope the claims, the Examiner is to determine whether there is "express, inherent or implicit support for the claim as a whole" (emphasis added). Applicants respectfully submit that the recitation of a range of 10.5 to 12.5 implicitly provides (to an objective person of ordinary skill in the art) a written description of the range about 10.5 to about 12.5.

In support of applicants' position, applicants note the decision reached in *BJ Services Co. v. Haliburton Energy Services Inc.*, Fed. Cir, 338 F3d 1368 (2003). In that case, the Federal Circuit held that one of ordinary skill in the art would understand that use of the term "about" is intended to encompass the range of experimental error that occurs in any measurement. Applicants' use of the term "about" is merely attempting the capture this range of error associated with measurements. The Examiner has failed to present any reasons why a person of ordinary skill in the art would not recognize that the written description of the invention provides support for the invention other than to note that the verbatim language is not included in the description. Such an analysis discounts the express guidelines provided by the US Patent Office to consider inherent or implicit support for the claim limitations. The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, that applicant was in possession of

the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. One of ordinary skill in the art recognizes that all measurements have a level of error (standard deviation) associated with them and that applicants' usage of the term "about" with regards to measurements of pH simply captures this expected variation.

Claim 15 is also objected to for the inclusion of the phrase "in the absence of a crosslinking agent." Applicants have replaced the objected terminology with the phrase "in the absence of covalent coupling." Support for this phrase is found in paragraphs [0003] and [0004] wherein applicants positively recite the term "covalent coupling" and distinguish that technique from "adsorption." More particularly, applicants note the disadvantages associated using covalent coupling to bind proteins to microparticles (see paragraphs [0004] and [0005]), and furthermore state that such coupling requires the use of hydrophilic surfaces. In paragraph [0022] applicants note that the present invention allows the use of hydrophobic particles, and the first sentence of the Summary of the Invention stresses that the object of the invention is to manufacture adsorptively loaded microparticles. Thus in the composition of the present invention, protein is adsorbed in the absence of covalent coupling.

The Examiner further objects to claim 15 for failing to recited that the recited size of the microparticles is "determined by photon correlation spectroscopy" and that failure to include such a limitation represents new matter. Applicants respectfully traverse the Examiner's objection, but in an effort to advance the prosecution of the present application, applicants have amended claim 15 to introduce the phrase as suggested by the Examiner.

Amended claim15 is believed to be fully compliant with the written description, and applicants request the withdrawal of the rejection of that claim under 35 USC 112, first paragraph.

Claims 13 and 17 are rejected as not meeting the written description requirement for the recitation of the range "about 0.3 to about 1.5 M" for the salt concentration. Applicants

note that the specification states at paragraph [0031] that one embodiment of the invention uses a salt concentration of 0.3 to 1.5 M. The Examiner contends that recitation of a range of "0.3 to 1.5 M" fails to support a range of "about 0.3 to about 1.5 M." As noted above with regards to the recited pH ranges, the term "about" is used in a manner consistent with common usage (see *BJ Services Co. v. Haliburton Energy Services Inc.*, Fed. Cir, 338 F3d 1368 (2003) to capture subject matter that is include within the standard deviation associated with such measurements. One of ordinary skill recognizes that any stated measurement value would inherently include some level of error, and thus a recited range of 0.3 to 1.5 M implies a range of about 0.3 to about 1.5 M. Accordingly, applicants respectfully submit the broader range of about 0.3 to about 1.5 M fully complies with the written description requirement of 35 USC 112, first paragraph.

Claims 9 and 18 are rejected for the use of the transitional phrase "consisting essentially of." Applicants respectfully traverse noting that such a transitional phrase is typically used in the field of biotechnology to indicate the possible presence of impurities that do not materially affect the basic properties of the claimed composition. However, to advance the prosecution of this matter applicants have removed the objected terminology, thus obviating this rejection.

Claims 9 and 18 also stand rejected for the use of the term "about" in defining the content of the microparticle. As noted above the inclusion of the term "about" is simply an effort by applicants to capture the experimental variance that is associated with any measurement. Applicants respectfully submit that one of ordinary skill would readily appreciate that applicants had possession of the claimed invention at the time the application was filed. In this regard applicants refer the Examiner to the US Guidelines for application of the Written Description (http://www.uspto.gov/web/menu/written.pdf), and in particular note the Decision Tree on page 6 of those Guidelines. When a claim amendment arguably

broadens the scope the claims, the Examiner is to determine whether there is "express, inherent or implicit support for the claim as a whole" (emphasis added). Applicants respectfully submit that the recitation of a microparticle having 88% polystyrene and 12% magnetite would be understood by those skilled in the art to include some variance in those listed percentages due to practical manufacturing techniques and experimental error associated with such measurements. Thus a recitation of a composition having 88% polystyrene and 12% magnetite would implicitly provide (to an objective person of ordinary skill in the art) a written description of the range about 88% polystyrene and about 12% magnetite.

In support of applicants' position, applicants note the decision reached in *BJ Services Co. v. Haliburton Energy Services Inc.*, Fed. Cir, 338 F3d 1368 (2003). In that case, the Federal Circuit held that one of ordinary skill in the art would understand that use of the term "about" is intended to encompass the range of experimental error that occurs in any measurement. Applicants' use of the term "about" is merely attempting the capture this range of error associated with measurements. The Examiner has failed to present any reasons why a person of ordinary skill in the art would not recognize that the written description of the invention provides support for the invention other than to note that the verbatim language is not included in the description. Such an analysis discounts the express guidelines provided by the US Patent Office to consider inherent or implicit support for the claim limitations. The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, that applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. One of ordinary skill in the art recognizes that all measurements have a level of error (standard deviation) associated with them and that applicants' usage of the term "about" with

regards to measurements of percentages of the microparticle components simply captures this expected variation.

The relevance of the Examiner's comments regarding the possibility that M-270 and M-280 beads may be functionalized is not understood by applicants. As noted in paragraph [0003] of the application "functionalized particles" are not "coated" but rather "These functional groups are used to form covalent bonds with the proteins, e.g., via amino or carboxy groups on the proteins to be coated". Only after proteins have been adsorbed or covalently coupled to the microparticle is the particle considered "coated." The claims simply require that the microparticles not be coated with a protein prior to the adsorption step, not that the microparticles be devoid of any functional groups.

Furthermore, the Examiner contends that applicants should be limited to only those microparticles that have the described properties and are specifically manufactured under the trademark of DYNABEADS. This over restrictive application of the written description requirement ignores the plain intent of applicants wherein the last sentence of paragraph [0022] specifically states:

> DYNABEADS from the DYNAL Company having a size ca 2.8 um and consisting of 88% polystyrene and 12% magnetite such as the hydrophobic beads M-280 or the epoxy beads M-270 are, **for example**, suitable. (emphasis added)

The clear intend of applicants was not to be limited to these two very specific examples of microparticles, but simply to give an example of the type of microparticles that would be suitable for use in the present invention. Again, the Examiner has failed to meet her burden of presenting any reasons why a person of ordinary skill in the art would not recognize that the written description of the invention provides support for the invention as claimed. One of ordinary skill would readily recognize that other beads having the recited properties and manufacture by someone other than the DYNAL company could be used in

the context of the present invention, and that applicants had possession of such additional embodiments at the time of the invention. Accordingly, claim 9 and are believed to fully comply with the written description requirement of 35 USC 112, first paragraph.

Claim 16 stands rejected for failing to meet the written description requirement for recitation of the phrase "about 4 to about 7 days." Applicants respectfully submit that the specification fully supports such a range, however in the interest of advancing the prosecution of the present application applicants have amended the claims to remove the objected language.

The amended claims are believed to fully comply with the written description, and applicants respectfully request the withdrawal of the rejection of claims 1-3, 5, 9, 11-13 under 35 USC 112, first paragraph as failing to comply with the written description requirement.

Claims 1-3, 5, 9 and 11-13 stand rejected under 35 USC 112, second paragraph as being indefinite. Applicants address each of the specific rejections as follows:

Claim 1 is rejected for the recitation of "alkaline conditions" together with the phrase "a pH selected from a range of about 10.5 to about 12.5." Applicants respectfully submit the recitation of the actual pH range simply refines what is meant by the term alkaline conditions, and is not indefinite. However to advance the prosecution of the present application applicants have amended claim 1 to remove the phrase "alkaline conditions" thus obviating the rejection.

Claim 20 is rejected for insufficient antecedent basis for the element "said coating step." Claim 20 has been amended to replace "coating step" with "incubating step." The amendment is believed to fully address the Examiner's rejection.

The amendments to claims 1 and 20 are believed to fully comply with 35 USC 112, second paragraph, and applicants respectfully request the withdrawal of the rejection of claims 1-3, 5, 9, 11-13 and 20 under that statutory section.

Claim 15 stands rejected as being anticipated by Kakabakos et al. Applicants respectfully traverse.

Kakabakos discloses adsorbing proteins onto a solid phase at a maximum pH of 9.6. In particular, they state, "For immobilization we immersed the beads in an approximate volume of protein coating solution, 0.5 mL per bead, then incubated them for 24 h at 22°C on the platform of an orbital shaker. We then washed the beads three times..." Applicants take issue with the Examiner's contention that a pH of 9.6 is within the range of "about" a pH of 10.0. A pH of 9.6 represents about 3.2×10^{-9} [H+], wherein a pH of 10.0 represents about 0.9×10^{-9} [H+]. Accordingly, a pH of 9.6 has approximately 4X as much [H+] as a solution at pH 10.5. Applicants respectfully submit that one of ordinary skill in the art would not consider a value 4X greater than another to be "about" the same. Accordingly, applicants respectfully submit the Examiner has failed to take into account the logarithmic nature of the pH scale when comparing the method of Kakabakos to applicants claimed method. This is an error one of ordinary skill in the art would not make, and thus the skill practitioner would readily comprehend that the Kakabakos reference fails to anticipate the claimed invention.

In addition, claim 15 has now been amended to recite that the pH range is from about 10.5 to about 12.5, thus further distinguishing the present invention over that of Kakabakos. The difference between Kakabakos' highest disclosed pH (9.6) and applicants lowest claimed pH value (10.5) represents approximately 8X difference in [H+] concentration. Accordingly applicants respectfully that Kakabakos fails to anticipate the invention of claim 15 and applicants request the withdrawal of the rejection of claim 15 under 35 USC 102.

Claims 15-20 stand rejected under 35 USC 103 as being unpatentable over Schmid in view of Vaynberg, Amiral et al and Lou et al. Applicants respectfully traverse.

Applicants note that the Schmid reference is in German and applicants were not provided a copy of the translation that the Examiner relied upon for the basis of her rejection. However, applicants have obtained a translation of the sections identified by the Examiner. Schmid discloses that while the coating step may be performed for 0-50 hours, it is preferable to conduct the coating step for up to 20 hours and most preferred to conduct such a step for 1 -20 hours. Thus while Schmid discloses a maximum incubation time that overlaps with applicants' shortest incubation times, an objective reading of the Schmid teaching clearly teaches away from the use of long incubation times, since the reference teaches a preference for incubation time of less than 20 hours.

Furthermore, the Schmid reference teaches that the mere adsorption step is not sufficient to obtain the desired coating results, and that a UV-irradiation step is absolutely necessary to achieve the desired coating of the microparticles. The Examiner contends that Schmid does not specifically mention the use of a "crosslinking agent" and there is nothing in the specification to indicate that UV light irradiation would be considered a crosslinking agent (or would induce the covalent coupling). Applicants respectfully submit that those skilled in the art readily appreciate that UV irradiation is a common technique used to crosslink materials. "Ultraviolet light is known to generate crosslinks between the complementary strands of DNA and between DNA and proteins (Photochem Photobiol. 1998 Apr;67(4):386-90). The lack of a specific reference to the UV irradiation step as inducing the formation of covalent bonds is likely due to the common understanding that crosslinking occurs during such a procedure. Accordingly, the reference specifically details the advantageous effects of UV irradiation after a preliminary coating step and that such UV irradiation is necessary to achieve sufficient coating results. One of ordinary skill would

assume that the formation of covalent couplings are required by the Schmid procedure. Interestingly, applicants have directly compared the results obtained using the method disclosed in Schmid with the present claimed method and surprisingly have found the claimed method provides superior results through the use of high pH without resorting to treatments that result in covalent coupling.

Schmid simply fails to teach or suggest the adsorption of a protein to polystyrene microparticles under strong alkaline conditions (e.g., pH of 10.5-12.5) for an extended period of time (e.g., 1-10 days or 4-7 days). The Examiner contends that, "it is known in the art that pH is a result-effective variable in the adsorption of proteins" as taught by Vaynberg et al, Amiral et al and Lou et al. Each of these references disclose that pH is one of many factors that impact the binding of materials to latex materials. However none of the references alone or together suggest a pH range as high as 10.5 to 12.5 should be used to adsorb proteins to microparticles.

In particular, the Examiner points to Amiral as disclosing that that increasing pH results in the stabilization of immunological reagents to be bound. However the Examiner but fails to mention that Amiral also discloses that raising the pH has negative effects as well:

> From a practical point of view, it is found that, irrespective of the buffer, increasing the pH and ionic strength results in a stabilization of the immunological reagent on the one hand and causes a proportional decrease in the reactivity on the other. (column 9, lines 45-50)

Applicants respectfully submit that the prior art must be considered in its entirety, including disclosure that teaches away from the claims (see MPEP §§ 2145(X)(D) and 2141.02 and *Mendenhall v. Astec Industries, Inc.*, 13 USPQ2d 1913, 1939 (Tenn. 1988), aff'd, 13 USPQ2d 1956 (Fed Cir 1989)). It is simply impermissible within the framework of 35 USC § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts. Accordingly, Amiral teaches that raising the

pH is a complex factor that has both positive and negative effects. Furthermore, Amiral is devoid of any suggestion of using the high pH ranges that are claimed in applicants' method. Amiral discloses a maximum pH range of 4-10, with a more preferred range of 8.2-8.5. Since Amiral state that raising the pH too high can have detrimental effects and lists a pH of 10.0 as the highest pH, the reference teaches away from using the high pH of applicants methods (i.e., pH 10.5-12.5).

Similar to the Amiral reference, the Vaynberg reference also fails to teach the pH range of applicants' invention. The Vaynberg reference discloses the adsorption of a polyampholyte gelatin onto colloidal matrices, including polystyrene, and the effect of various parameters on gelatin adsorption. Vaynberg focuses on conditions that maximize the loading of gelatin on the various particles but fails to provide any information regarding the stability of their compositions. There is no data presented or any discussion regarding conditions that will reduce bleeding from the formed compositions. Accordingly, Vaynberg fails to provide any direction to one skilled in the art with regards to a procedure that optimizes the stability of microparticles that comprise adsorbed proteins.

Applicants have discovered that incubating the microparticles and the protein at an alkaline pH for long periods of time (1 to 10 days) produces optimally stabilized compositions. Vaynberg provides no such information or any suggestion that would direct one to use such long incubation times at pH of 10.5 to 12.5.

First of all, Vaynberg explicitly teaches that the maximum adsorption of gelatin is obtained at around pH 6.2 for coating of polystyrene particles (p. 469, left column, lines 5-7). This value is far removed from the highly alkaline (pH 10.5-12.5) levels used in the claimed invention and the reference provides no teaching or suggestion that increasing the pH would have any impact with regards to adsorption of proteins and enhanced stability of those compositions. The Examiner contends that applicants have taken this statement of Vaynberg

out of context and that other sections of the reference state that pH differences were "not critical" and "produced little variation" in the adsorption efficiency of gelatin onto the polystyrene (p. 469, right column, l. 25 to p. 470, left column and Figs. 2-3).

Applicants respectfully submit that the statement on page 469, left column, lines 5-7 speaks for itself and that the authors clearly stated "In contrast, [to the effects observed with acrylic latex] the effect of pH on gelatin adsorption to PS [polystyrene] is noticeably weaker, with a maximum around pH 6.2". This statement is clearly directed to the interactions between pH and the adsorption of a protein to a polystyrene microparticle. Regardless of more generic statements made in the reference noting that the overall impact of pH on adsorption was minimal, the authors specifically state that a maximum effect was obtained at pH 6.2 for polystyrene microparticles. The meaning of this statement needs no further interpretation, and the surrounding text does not change the explicit meaning of the statement.

At the very least, an objective reading of Vaynberg's statement (and the surrounding text) fails to provide any motivation for one to test the effect of pH at the high alkaline range of 10.5 to 12.5, since changes in pH, if having any effect at all, has a maximum effect at the acidic pH of 6.2. Furthermore, applicants respectfully submit that the Vaynberg objective teaching actually discourages one from testing strong alkaline conditions as such conditions would cause a drop in absorption (however minimal that effect may be), and thus the objective teaching teaches away from applicants' invention which uses a strong alkaline pH. In fact the statements provided by Amiral support the contention that raising the pH above a certain threshold will produce detrimental effects outweighing the benefits of a higher pH. Therefore applicants respectfully submit that the combined teaching of Vaynberg and Amiral actually lead one away from the use of pH ranges higher than 10.0, as applicants have done and now claim as their invention.

The last reference cited by the Examiner (Lou et al) in the combination of references used to reject claims 15-20 under 35 USC 103, also fails to complement the inadequacies of the Schmid, Vaynberg and Amiral teachings with regards to the claimed method.

Lou et al. discloses a method of adsorbing a protein (streptolysin-O) onto a polystyrene latex particle. However, Lou also teaches that a crosslinking agent (carbodiimide) must be used to obtain a stable composition. As stated in the first sentence of the Detailed Description:

> A significant feature of the present invention is embodied in a complex consisting of polystyrene latex particles adsorbed with streptolysin-O antigen in an alkaline environment, the adsorption occurring in the presence of carbodiimide. (emphasis added)

The application repeatedly states the importance of crosslinking the adsorbed proteins to stabilize the final product (see column 4, lines 34-48). Thus Lou et al, consistent with the teachings of Kakabakos et al, teach away from the present invention which provides a method for producing a stable coated microparticle in the absence of covalent coupling (i.e. crosslinking). To clarify this distinguishing characteristic of the present invention, applicants have amended claim 1 to use the closed transitional language "consisting of", and have amended claim 15 to specifically exclude the use of covalent coupling in the claimed method. Lou et al. fails to teach or suggest that a stable composition can be formed by adsorbing proteins onto a polystyrene microparticle in the absence of further covalent coupling.

Moreover, since Lou et al teach that such a crosslinking step is conducted "in conjunction with" the adsorption step and is necessary to achieve stability, the reference teaches away from the present invention which specifically excludes the use of such a crosslinking step. Lou et al also fails to teach or suggest the long incubation times that are used in applicants' process to produce the stabile coated microparticles. Accordingly,

applicants respectfully submit that Lou et al fails to supplement the inadequacies of the Schmid, Vaynberg and Amiral references.

The Examiner repeatedly attempts to discount the inadequacies of the prior art teaching by broadly applying the notion that the missing element represents a "result-effective variable." (see the Office Action of May 2, 2007 at page 21, lines 3-6 with regards to pH; page 22, lines 5-7 with regards to incubation times; page 22, lines 16-18 with regards to ionic strength). Applicants respectfully submit that optimization of a procedure can only occur when there is guidance as to what parameters should be varied to produce the optimal result. As noted above, both the Vaynberg and Amiral references state that high pHs can cause detrimental effects. Similarly, both the Lou and Schmid references teach the importance of crosslinking the material to produce the desired stability. This additional step of crosslinking the material substantially distinguishes those methods from the present invention and the methods of Vaynberg and Amiral.

Since Lou and Schmid obtained their composition through the use of an additional covalent linkages step there is no reasonable expectation that one could select one of the parameters disclosed in Schmid and apply that one parameter to the Vaynberg teaching to generate the same result as obtained by the entirety of the Schmid procedure. Furthermore, Schmid states a preference for shorter incubations times of 20 hours or less thus teaching away from the use of long incubation times of 1-10 days as applicants now claim.

The cited references for all their combined teachings fail to teach or suggest that raising the pH above 10.0 and extending incubation times would lead to an optimized method of preparing stabilized protein adsorbed microparticles. While it may be obvious to alter all parameters that are known to impact adsorption of proteins (i.e. ionic concentration, pH, temperature, crosslinking agents...) until arriving at applicants invention, the prior art must provide some indication of which parameters are critical, or which of the possible choices

would lead to success, for a finding of obviousness. The cited references fail to teach, and provide no guidance for selecting, the specific parameters of pH and length of incubation that applicants have done and now claim as their invention for producing the surprisingly stable protein adsorbed microparticles.

Applicants have demonstrated that their unique combination of selected conditions, using ranges outside those taught or suggested by the prior art has produced a surprisingly improved composition. In particular the data present in Figs. 3 and 4 shows the vast improvement in the homogenous distribution of the coated beads with lower proportions of dimeric, trimeric and higher aggregates compared to those obtained by the prior art methods (i.e. those of the Schmid reference) as indicated in Fig. 2. The beads prepared by applicants' methods also have surprisingly low bleeding rates, below 150 ng/mg and in most cases even less than 100 ng/mg after stress.

Applicants respectfully submit claims 15-20 are patentable over the combined teaching of Schmid, Vaynberg et al, Amiral et al and Lou et al and applicants respectfully request the withdrawal of the rejection of those claims under 35 USC 103.

Claims 16-17 and 20 stand rejected under 35 USC 103 as being unpatentable over Kakabakos et (in light of Song) in view of Amiral et al.

The deficiencies of the Kakabakos references in terms of its failure to teach applicants' claimed pH range has been noted above. Kakabakos teaches a maximum pH of 9.6, whereas claims 16 and 17, which depend from claim 15, require a minimum pH of 10.5. The Examiner contends that the secondary reference teaches that the duration of the reaction is one experimental condition that can be adjusted. However the generic statement of Amiral that "the experimental conditions, namely the pH, the ionic strength, the volume, the temperature, the duration and the concentration of the ligand, are adjusted according to the nature of the product to be assayed..." fails to provide sufficient guidance to make applicants'

invention obvious. Amiral lists six different conditions that can be varied, without stating how any relate to one another or without giving any guidance how they should be modified. Such a broad generic statement is simply an invitation to experiment and fails to provide sufficient guidance to suggest applicants' unique combination of conditions that provide for a superior product.

The Examiner also contends that Kakabakos also teaches immobilization of IgG onto polystyrene beads increases as a function of time, citing the data presented in Fig. 2 and the paragraph bridging pages 943 and 949. However, applicants note that Fig. 2 is labeled "Temperature effect on the rate of immobilization of IgG onto polystyrene beads at pH 9.6" (emphasis added). Furthermore, the referenced paragraph is entirely directed to the impact of temperature on IgG immobilization. Lastly, applicants note that Fig. 2 indicates that at least 90% (even more for ethanol treated beads) of immobilization occurs in less than 5 hours. Although error bars are not included on the graph, applicants question whether the slight increase in bound IgG shown post 20 hours is statistically significant. Applicants respectfully submit that a careful, objective reading of the cited prior art would not lead one to applicants' claimed invention.

Claims 16-17 and 20 are believed to be patentable over the cited Kakabakos et (in light of Song) and Amiral et al references. Accordingly applicants request the withdrawal of the rejection of those claims under 35 USC 103.

Claim 18 stands rejected under 35 USC 103 as being unpatentable over Kakabakos et (in light of Song) in view of Amiral et al in further view of Bangs and Gudiband et al. Applicants respectfully traverse this rejection.

Claim 18 depends from claim 16 which in turn depends from claim 15. Claim 18 therefore incorporates all the limitations of claims 15 and 16. The additional cited Bangs and Gudiband et al references fails to supplement the teaching of Kakabakos et al and Amiral et

al with regards to applicants' claimed pH range and duration of incubation. Accordingly, claim 18 is believed patentable over the cited references for the same reasons recited above regarding the patentability of claims 15 and 16.

The foregoing claim amendments and remarks are believed to fully respond to the Examiner's rejections and the claims are believed to be in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance. If any further discussion of this matter would speed prosecution of this application, the Examiner is invited to call the undersigned at (434) 220-2866.

Respectfully submitted,

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